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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,996	05/24/2000	Mark T. Keating	HYDR-P01-002	4041

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,996	KEATING ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-14,22-24,26-33,35,48-50,56-63,65 and 67-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-14,22-24,26-33,35,48-50,56-63,65 and 67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Upon further consideration of the amendment filed 2-9-05, the finality of the Official action mailed 6-7-04 has been withdrawn.

Claims 22 and 30 have been amended. Claims 5 and 25 have been canceled. Claims 1-4, 6-14, 22-24, 26-33, 35, 48-50, 56-63, 65 and 67-69 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4, 6, 7, 9-14, 22-24, 26, 28-33, 35, 48, 50, 56-62, 67 and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a bioactive fragment of SEQ ID NO. 3 having six repeats of a hexameric sequence of SEQ ID No. 1, does not reasonably provide enablement for using a bioactive fragment of SEQ ID NO. 3 having sseven repeats of a hexameric sequence of SEQ ID No. 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-4, 6, 7, 10-14, 22-26, 28-33, 35, 48, 50, 56-62, 67 and 68 read on an elastin-based composition comprising a polypeptide comprising a bioactive fragment of SEQ ID No. 3 that includes seven repeats of the hexameric sequence of SEQ ID No. 1, and the use of said composition. The amino acid sequence of SEQ ID No. 3 as disclosed in the specification (e.g. p. 48) only contains six hexameric sequence of SEQ ID No. 1, i.e. VGVAPG. Since the sequence

of SEQ ID No. 3 only has six repeats of VGVAPG, a bioactive fragment of SEQ ID No. 3 could not have included seven repeats of VGVAPG. The specification fails to provide enabling disclosure for the preparation and use of an elastin-based composition comprising a polypeptide comprising a bioactive fragment of SEQ ID No. 3 that includes seven repeats of the hexameric sequence of SEQ ID No. 1. Therefore, one skilled in the art at the time of the invention would not know how to make and/or use an elastin-based composition comprising a polypeptide having a bioactive fragment of SEQ ID No. 3 containing seven repeats of VGVAPG, wherein said composition has one or more biological activities as recited in the claims. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

3. Claims 22-24, 26-33 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a tropoelastin or 7 repeats of the sequence of SEQ ID No. 1 (VGVAPG) or a method for preventing vascular restenosis by using said composition *in vitro* or via direct administration of said composition to a targeted site *in vivo*, does not reasonably provide enablement for a method for prophylaxis of a restenosis having diminished capacity to regulate smooth muscle cell function, by delivering said pharmaceutical composition to a targeted site via various administration route other than direct administration *in vivo,* or a method for treatment of a restenosis by delivering said pharmaceutical composition to a targeted site via any administration route in vivo, such as via a biocompatible support. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 22-24, 26-33 and 35 are directed to a method for prophylaxis or treatment of a restenosis having diminished capacity to regulate smooth muscle cell function by delivering a pharmaceutical composition that provides an elastin-based composition comprising a polypeptide comprising an amino acid sequence at least 95% identical to SEQ ID No. 3, or a fragment including at least six or seven hexameric sequence of SEQ ID No. 1, to a target site *in vivo*, wherein said composition has one or more biological activities of inhibiting proliferation, stimulating differentiation, or regulating migration of smooth muscle cells *in vivo* or binding to smooth muscle cells. Claim 26 specifies said elastin-based composition comprises a recombinant polypeptide. Claim 27 specifies said elastin-based composition comprises a synthetic elastin peptide comprising 6 repeats of VGVAPG. Claim 29 specifies the composition comprises an elastin matrix produced from a blood vessel. Claims 30 and 31 specify the composition is attached to a biocompatible support. Claim 33 specifies the elastin-based composition is delivered directly to a vascular site.

The claims read on using a pharmaceutical composition comprising a polypeptide comprising an amino acid sequence at least 95% identical to SEQ ID No. 3, a bioactive fragment of SEQ ID No. 3 having at least six or seven repeats of SEQ ID No. 1, or a peptide fragment having six or seven repeats of SEQ ID No. 1, to prevent or treat restenosis via various administration routes *in vivo*. The term "biocompatible support" is interpreted as any material that is biocompatible, for example, water, saline solution, sucrose, polysaccharide, collagen and other biocompatible polymers etc. The specification discloses use of a human tropoelastin or 7

repeats of the sequence of SEQ ID No. 1 (VGVAPG) for preventing vascular restenosis *in vitro* or *in vivo*.

The specification fails to provide adequate guidance and evidence for how to use the claimed pharmaceutical composition to prevent restenosis via various administration routes other than direct coronary artery administration, or to treat restenosis via any administration route in vivo, so as to provide therapeutic effect in treating or preventing restenosis *in vivo*. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101, IDS) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). Similarly, the amount and the stability of the protein delivered, the degradation of the protein during the process of reaching its target site, and the protein's compartmentalization within the cell are important factors in determining the efficiency of protein delivery in vivo. It was known in the art that administration route of a pharmaceutical composition plays an important role in the efficiency of said composition *in vivo*. The type of administration route determines how the claimed elastin-based composition reaches its targeted site *in vivo*. The location of administration, the amount and stability of the polypeptides or peptides *in vivo*, and its compartmentalization within the cell determine whether sufficient polypeptides or peptides can

reach their target site so as to provide therapeutic effects for preventing or treating restemosis *in vivo*.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 6-8, 10, 12, 48, 49, 60, 61, 63, 65 and 69 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Weiss A. S., 1999 (WO 99/03886).

Claims 1-4, 6-8, 10, 12, 48, 49, 60, 61, 63, 65 and 69 are directed to a pharmaceutical composition that provides an elastin-based composition for localized delivery in vivo,

comprising a polypeptide having (i) an amino acid sequence at least 95% identical to SEQ ID No. 3, (ii) a bioactive fragment of SEQ ID No. 3 that includes six or seven repeats of SEQ ID No. 1, or (iii) a peptide fragment consisting essentially of six or seven repeats of SEQ ID No. 1, wherein said composition is attached to a biocompatible support or dissolved in a biocompatible matrix and has one or more biological activities as recited in the claims.

Weiss discloses a nucleotide sequence encoding human tropoelastin derivative SHELdelta26A in Figure 2, which comprises six repeats of VGVAPG (SEQ ID No. 1) (see computer printout pages 7-8), and the human tropoelastin derivative has elastin-like properties and macro-binding properties. The human tropoelastin derivative can be prepared in a formulation together with a pharmaceutically acceptable carrier or diluent (e.g. p. 50, 56), or chemically or enzymatically cross-linked to form implants (e.g. p. 16-17). The biological activities recited in the claims are considered inherent to the disclosed human tropoelastin derivative. Thus, claims 1-4, 6-8, 10, 12, 48, 49, 60, 61, 63, 65 and 69 are either anticipated by or, in the alternative, are obvious over Weiss.

7. Claims 1-4, 6-8, 10-12, 48, 49, 60, 61, 63, 65 and 69 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Rothstein et al., 1998 (WO 98/05685).

Claims 1-4, 6-8, 10-12, 48, 49, 60, 61, 63, 65 and 69 are directed to a pharmaceutical composition that provides an elastin-based composition for localized delivery in vivo, comprising a polypeptide having (i) an amino acid sequence at least 95% identical to SEQ ID No. 3, (ii) a bioactive fragment of SEQ ID No. 3 that includes six or seven repeats of SEQ ID

No. 1, or (iii) a peptide fragment consisting essentially of six or seven repeats of SEQ ID No. 1, wherein said composition is attached to a biocompatible support or dissolved in a biocompatible matrix and has one or more biological activities as recited in the claims. Claim 11 specifies the elastin-based composition comprises an elastin matrix produced from a blood vessel.

Rothstein discloses a nucleotide sequence encoding human elastin derivative containing minimal functional unit-1 (MFU-1) in Figure 1B, which comprises six repeats of VGVAPG (SEQ ID No. 1) (see computer printout pages 9-10), and the human elastin derivative can be used in prostheses that are implanted into humans. The human elastin derivative can be prepared in a prostheses comprising a metal coated with the human elastin derivative, a material suitable for implantation into human, and a cosmetic materials (e.g. p. 31). Rothstein teaches mixing radio-labeled human MFU-1 with chicken elastin matrix isolated from chicken aortic tissue in PBS buffer and shows that the MFU-1 coated chicken elastin matrix displayed enhanced surface auto-flyorescence and suggesting a complete and continuous coating of the matrix by MFU-1 (e.g. example 4). The biological activities recited in the claims are considered inherent to the disclosed human elastin derivative. Thus, claims 1-4, 6-8, 10-12, 48, 49, 60, 61, 63, 65 and 69 are either anticipated by or, in the alternative, are obvious over Rothstein.

It should be noted that a declaration showing that those biological functions recited in the claims are not inherent to the claimed elastin-based composition would overcome the art rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER